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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/529,795	04/20/2000	HARTMUT KUPPER	0480/001178	4157

26474 7590 04/22/2002

KEIL & WEINKAUF
1350 CONNECTICUT AVENUE, N.W.
WASHINGTON, DC 20036

EXAMINER
SEHARASEYON, JEGATHEESAN

ART UNIT	PAPER NUMBER
1647	8

DATE MAILED: 04/22/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/529,795	Applicant(s) KUPPER ET AL.	
	Examiner Jegatheesan Seharaseyon	Art Unit 1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 February 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. This office action is in response to the amendment and response filed on 2/04/02 in Paper No: 7. Claims 1-7 are pending.

2. Applicants have amended the specification to include section headings and a detailed description of the drawings.

3.The text of those sections of Title 35, U. S. Code not included in this action can be found in a prior Office action.

35 USC § 112, second paragraph and 101 rejections are withdrawn

4. Rejection of claims 1-4 for reciting a use without setting forth any steps involved in the method or process of that use is withdrawn in light of applicant's amendment.

5. Applicant's amendments have obviated the rejection regarding vague and indefinite language used in claims 4 and 5. Specifically applicants have substituted the term "kit" for "commercial pack".

35 USC § 102, rejection is withdrawn

6. Applicants arguments are persuasive and thus the rejection of claims 1-4 and 7 under 35 USC § 102(e) as anticipated by Stenzel et al. (US Pat No: 6, 235, 281) are withdrawn.

7. The previous rejection of claims 4 and 5 under 35 U.S.C. 103(a) is withdrawn in favor of the new 103(a) rejection over claims 1-7.

Claim Rejections - 35 USC § 103

8. Claims 1-7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Stenzel et al. (U.S. Patent No: 6,235,281).

The instant invention is directed to the use of TNF antagonists for the production of drugs for the treatment of septic disorders characterized by elevated serum levels of interleukin-6 (IL-6).

Stenzel et al. teaches a method of treating a patient with septicemia (a septic disorder) with elevated IL-6 levels (above 1000pg/ml) by administering TNF antagonist. They also teach that the TNF antagonist used is a $F(ab')_2$ fragment of a monoclonal anti-TNF antibody (column 3, lines 39-40). Please note that the examiner is considering, in view of the specification, the IL-6 levels indicated in claim 1 of U.S. Patent No: 6,235,281 to be 1000pg/ml and not 1.000p/ml. The levels of IL-6 in '281, are clearly above the 500pg/ml threshold of the instant claims. In addition, Patent '281 teaches that a distinct reduction in mortality is observed when the septicemia patients who are treated have IL-6 levels of 500 pg/ml or more at the start of the treatment (column 2, lines 17-19).

However, they do not describe the change in serum IL-6 level after a measurement period of at least 30 minutes and a mathematical description of the change over time of the level of IL-6. They also do not describe a commercial pack for the use in treatment of septic disorder. It is routine in the management of patients with chronic conditions to monitor proinflammatory cytokines (IL-6) as markers over a period of time to determine the change in the levels. This change in IL-6 levels can be measured by a routine mathematical description of the change over time of the level of IL-6. Furthermore, it would have been obvious to package the antagonist into a kit for the routine commercial exploitation of the invention for treating septic disorders.

Therefore, the instant invention is prima facie obvious over Stenzel et al. (U.S. Patent No: 6,235,281).

Double Patenting Rejection maintained

9. Applicant's arguments have been fully considered but are not persuasive. Patent '281 indicates that a clear correlation of treatment with TNF antagonists to increased IL-6 levels (column: 2 lines 15-21). Patent '281 teaches that the treatment is deemed successful (distinct reduction in mortality), when the septicemic patients who have IL-6 levels of 500 pg/ml or more at the start of the treatment. It further states that patients who have IL-6 serum levels above 1000 pg/ml profit particularly well from the treatment. Although, the measurement period is not indicated, the change in level is clearly indicated. Thus, claims 1-7 are obvious over claims 1-3 of Stenzel et al. (U.S. Patent No: 6,235,281).

New Claim Rejections - 35 USC § 112

10. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10a. Claims 1-3 and 5-7 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. *This is a written description rejection.*

The specification recites the use of murine anti-TNF antibody fragment (Mab 195F) to treat sepsis. However, the specification does not disclose all TNF antagonists. The claims as written, however, encompass TNF antagonists which were not originally contemplated and fail to meet the written description provision of 35 USC 112, first paragraph because the written description is not commensurate in scope with the recitation of claims 1 and 4-7. The specification does not provide written description for all TNF antagonists. *Vas-Cath Inc. v. Mahurkar*, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed" (*See Vas-Cath* at page 1116). Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 USC 112 is severable from its enablement provision. (See page 1115.)
With the exception of an anti-TNF antibody fragment (MAb 195) which is capable of treating patients with sepsis (see pages 5 and 6), the skilled artisan cannot envision all the detailed structure of the claimed compounds (TNF antagonists), regardless of the complexity or simplicity of the method isolation. As a result, it does not appear that the inventors were in possession of invention to use all SCAP antagonists set forth in claims 1-3 and 5-7. Claims 2 and 3 are rejected insofar as they are dependent on rejected claim 1.

10b. Claims 1-3 and 5-7 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the treatment of sepsis with TNF antibody (MAb 195F), does not reasonably provide enablement for treating septic disorders with all TNF antagonist. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. See *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 The factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue" include, but are not limited to: (1) the breadth of the claims; (2) the nature of the invention; (3) the state of the prior art; (4) the level of one of ordinary skill; (5) the level of predictability in the art; (6) the amount of direction provided by the inventor; (7) the existence of working examples; and (8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure.

The specification as filed is insufficient to enable one skilled in the art to practice the claimed invention without an undue amount of experimentation. Applicants have demonstrated that using a MAb 195F they are able to treat severe sepsis. There is no evidence provided in the specification regarding other antagonist able treat severe sepsis or other septic disorders. Applicant recites a broad, arbitrary, class of compound (TNF antagonist) to treat a broad class of diseases (septic disorders). Since applicant

has not provided any working examples of the efficacy of TNF antagonist in treating already established disease subjects or applicable models, it would require an undue amount of experimentation to one of skill in the art to practice the claimed invention.

Given the breadth of claims 1 and 5-7 in light of the unpredictability of the art as determined by the lack of working examples, the level of skill of the artisan, and the lack of guidance provided in the instant specification and the prior art of record, it would require undue experimentation for one of ordinary skill in the art to make and use the claimed invention to treat septic disorders using the TNF antagonist. Claims 2 and 3 are rejected insofar as they are dependent on rejected claim 1.

11. No Claims are allowable.

Contact Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jegatheesan Seharaseyon whose telephone number is 703-305-1112. The examiner can normally be reached on M-F: 8:30-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz can be reached on 703-308-4623. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-0294 for regular communications and 703-308-4227 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

JEFFREY STUCKER
PRIMARY EXAMINER